REMARKS

Reconsideration of the objection to or rejection of all claims is respectfully requested in view of the above amendments and the following remarks.

Claim Amendments

Claim 39 has been amended to delete the recitation of "or prodrug" in an effort to expedite the prosecution of this application, without waiver or prejudice to Applicants' right to prosecute claims to prodrugs *per se* in a continuing application, and without prejudice to Applicants' rights under applicable law to assert infringement of the amended claims under principles of inducement, contributory infringement or the doctrine of equivalents, where a compound falling within the literal scope of the claims is formed by administration of a prodrug.

Claim 39 has been further amended to incorporate the more specific definition of Ring C from claim 42, and claim 42 has been cancelled as now being redundant.

Claim 45 has been amended to remove "hydrogen" from the moieties excluded by the proviso, in that hydrogen is already excluded from the definition of R^2 by the proviso at the end of claim 39.

The dependency of pharmaceutical composition claim 51 has been expanded to include any one of compound claims 39-41, 43-48 and 61, and the reference to "formula I" has been corrected to refer to formula II.

Method claim 62 has been cancelled, and new method claim 63 has been added, directed toward inhibiting VEGF receptor tyrosine kinase activity in a warm blooded animal by administration of a compound of the formula (II) as claimed in claim 39. Support and

enablement for the claimed inhibition of VEGF receptor tyrosine kinase activity is found, *e.g.*, at specification page 84, lines 6-8 and in assay procedures (a) through (c) disclosed at specification page 80, line 11 through page 83, line 16.

Following entry of these amendments claims 39-41, 43-49, 51, 61 and 63 remain pending in this application.

Claim Status

Prior to entry of the above amendments, claims 46-48 and 61 have only been objected to as being dependent on a rejected claim. Claims 39-45, 49 and 51 have been rejected for various grounds under section 112, and claims 39-41, 43, 44, 49 and 51 have also been rejected as being obvious over the Schaper '009 patent. All grounds for rejection are respectively traversed, and are believed to have been overcome by the above amendments and/or the following remarks, thereby placing this application in condition for allowance.

Claim Rejection – 35 USC § 112 – "prodrug"

Claim 39 has been rejected under 35 U.S.C. § 112, first and paragraphs, on the assertion that there is insufficient written description for the claim term "prodrug." The term "prodrug" is used throughout the present specification, for example at page 52, lines 16-17, with the guidance that the intended prodrugs are, "for example esters, amides and sulphides, preferably esters and amides." Moreover, the term "prodrug" has traditionally been allowed in pharmaceutical claims under U.S. practice without question for well over a decade. The widespread acceptance of the term "prodrug" over this period constitutes recognition that persons skilled in the art have no difficulty in understanding the scope and intended meaning of the term, and the extensive use of this term in pharmaceutical patents and literature itself

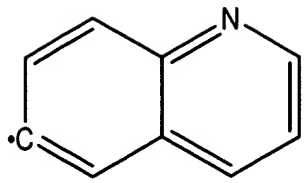
provides a wealth of information and guidance in this art that should refute these section 112 grounds for rejection.

Nevertheless, in order to expedite the prosecution of this application to allowance, the term "prodrug" has been removed from claim 39, without prejudice to applicants' right to prosecute claims to prodrugs *per se* in a continuing application. Moreover, this amendment is being made without prejudice to Applicants' rights under applicable law to assert infringement of the amended claims under principles of inducement, contributory infringement or the doctrine of equivalents, where a compound falling within the literal scope of the claims is formed by administration of a prodrug.

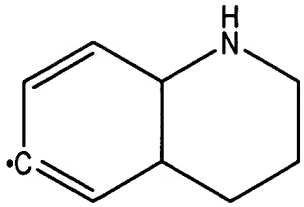
Claim Rejection – 35 USC § 112 – Ring C

Claims 39-45 and 49 have been rejected under section 112, first paragraph, for insufficient written description, and claims 39-45, 49, 51 and 62 have been rejected under section 112, second paragraph, for lack of enablement, with respect to the definition of ring C. The Examiner asserts that the specification does not describe bicyclic or tricyclic moieties for Ring C, other than quinoline and indoline, or how to prepare and use compounds of formula II wherein ring C is other than quinoline or indoline. These grounds for rejection are respectively traversed.

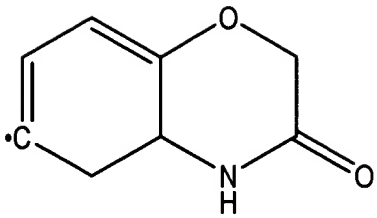
First of all, the assertion that only quinoline and indoline C-ring structures are described and enabled overlooks the fact that a number of other bicyclic and tricyclic C-ring structures are actually exemplified in the specification. These include the C-ring structures depicted below, which are a part of at least one compound in the Examples, as indicated:



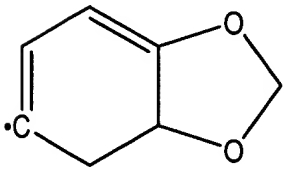
Ex 1: quinolin-6-yl



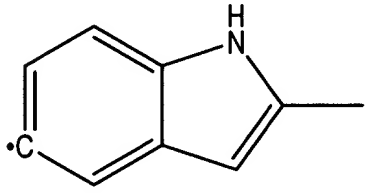
Ex 192: 1,2,3,4-tetrahydroquinolin-6-yl



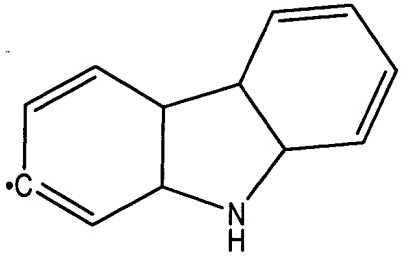
Ex 19: 3-oxo-2H-4H-1,4-benzoxazin-6-yl



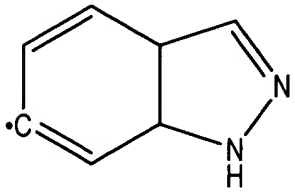
Ex 24: 1,3-benzodioxol-5-yl



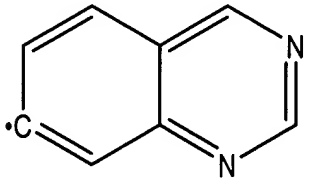
Ex 11: 2-methylindol-5-yloxy



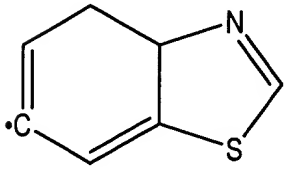
Ex 200: 9H-carbazol-2-yl



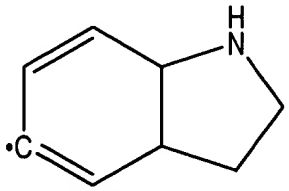
Ex 25: 1-H-indazol-6-yl



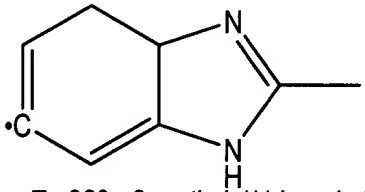
Ex 324: quinazolin-7-yl



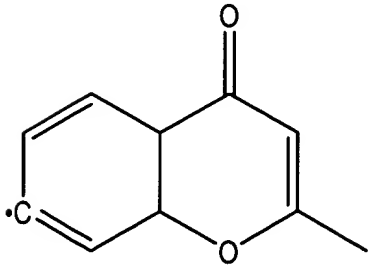
Ex 27: 1,3-benzothiazol-6-yl



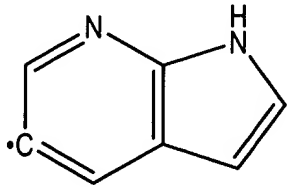
Ex 194: 2,3-dihydro-indol-5-yl



Ex 323: 2-methyl-1H-benzimidazol-6-yl



Ex 30: 2-methyl-4-oxo-4H-chromen-7-yl



Ex 182: 1H-pyrrolo[2,3-b]pyridin-5-yl

It is thus clear that the compounds actually exemplified in the specification encompass 9, 10 and 13-membered ring structures having heteroatoms selected from O, N and S. The specification includes a written description of a scope of compound that encompasses the full scope of the ring-C recitation in claim 39 (see, *e.g.*, page 3, lines 13-15), as well as the representative exemplification illustrated above.

Nevertheless, in an effort to expedite the prosecution of this application to allowance, the above amendments incorporate the more preferred claim 42 definition of C-ring into independent claim 39, and claim 42 has been cancelled. This amendment is made without prejudice to Applicants' right to prosecute a broader scope of C-ring definition in a continuing application. This more preferred definition of the C-ring is also described in the specification, *e.g.*, at page 12, lines 28-29. Thus, the definition of the C-ring in amended independent claim 39 is now "a 9 or 10-membered heteroaromatic bicyclic moiety which contains 1-3 heteroatoms selected independently from O, N and S." It is respectfully submitted the specification exemplifies a sufficient number of compounds, as illustrated on the preceding page, which represent a variety of C-ring structures throughout this preferred definition, so as to amply meet the written description and enablement requirements of section 112. Therefore, it is respectfully submitted that this ground for rejection has been overcome.

Claim Rejection – 35 USC § 112 – indefiniteness

Claims 45 and 62 have been rejected under section 112, second paragraph, as being indefinite.

This rejection of claim 45 is based on an assertion that claim 45 "lacks antecedent basis because the proviso for R^2 not to be 'substituted or unsubstituted C_{1-5}alkyl, halogeno, C_{1-5}alkoxy, C_{2-5}alkenyl, phenoxy or phenylC_{1-5}alkoxy' does not have antecedent basis in claim 39." This ground for rejection is respectfully traversed.

Claim 45 as amended above provides for:

> A compound according to claim 39 wherein Zb is -O-, with the proviso that R^2 is not substituted or unsubstituted C_{1-5}alkyl, halogeno, C_{1-5}alkoxy, C_{2-5}alkenyl, phenoxy or phenylC_{1-5}alkoxy.

Claim 39 defines a compound of formula II, wherein Zb is defined as "–O– or –S–." Clearly independent claim 39 provides antecedent basis for Zb being further limited to –O–. Similarly, claim 39 defines the group R^2 as being a number of possible moieties:

- R^2 = substituted or unsubstituted C_{1-5}alkyl is found, *e.g.*, in the second paragraph of claim 39 wherein R^2 represents the group R^5X^1–, wherein X^1 is a direct bond, and the definition of R^5 in subparagraph 1) includes substituted or unsubstituted C_{1-5}alkyl;
- R^2 = halogeno is found, *e.g.*, in the first paragraph of the claim 39 definition of R^2;
- R^2 = C_{1-5}alkoxy is found, *e.g.*, in the second paragraph of claim 39 wherein R^2 represents the group R^5X^1–, wherein X^1 is –O–, and the definition of R^5 in subparagraph 1) includes C_{1-5}alkyl;
- R^2 = C_{2-5}alkenyl is found, *e.g.*, in the second paragraph of claim 39 wherein R^2 represents the group R^5X^1–, wherein X^1 is a direct bond, and the definition of R^5 in subparagraph 18) includes C_{2-5}alkenyl;

- R^2 = phenoxy is found, *e.g.*, in the second paragraph of claim 39 wherein R^2 represents the group R^5X^1–, wherein X^1 is –O–, and the definition of R^5 in subparagraph 9) includes R^{29}, where R^{29} can be a phenyl group; and
- R^2 = phenylC_{1-5}alkoxy is found, *e.g.*, in the second paragraph of claim 39 wherein R^2 represents the group R^5X^1–, wherein X^1 is –O–, and the definition of R^5 in subparagraph 10) includes C_{1-5}alkylR^{29}, where R^{29} can be a phenyl group.

Thus there is antecedent basis for the *inclusion* of each of the groups recited in the claim 45 proviso, so there clearly is antecedent basis for their *exclusion* in narrower, dependent claim 45. In addition, there is clear support for the proviso of claim 45 and the exclusion of these specific values for R^2 from the compound scope. In this regard, the Examiner's attention is drawn to *original* claim 15, which was dependent on *original* independent claim 9, which defined compounds of formula II. Independent claim 39 (defining compounds of formula II) and claim 45 (dependent on claim 39) were added by the Preliminary Amendment filed May 6, 2002, at the same time that original independent claim 9 (defining compounds of formula II) and claim 15 (dependent thereon), were cancelled. In addition, support for the proviso of claim 45 is found in the original specification at page 53, lines 25-26.

Upon consideration of the foregoing, it is clear that there is both antecedent basis in claim 39 for the groups excluded by the proviso of dependent claim 45, and support for the proviso of claim 45, in this application as originally filed. Therefore, withdrawal of this ground for rejection is respectfully requested.

Claim Rejection – 35 USC §103

Claims 39-41, 43, 44, 49 and 51 have been rejected under section 103(a) as being unpatentable over Schaper '009. Specifically, the Examiner asserts that Tables 9 and 10 of the reference

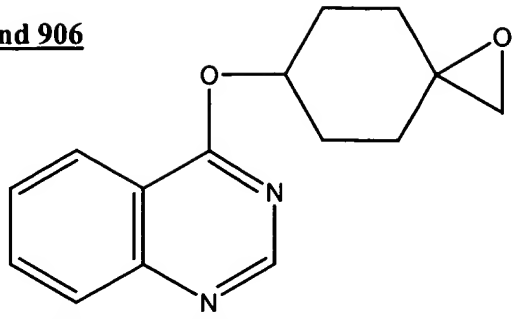
> ". . .list some substituted quinazolinyl compounds (e.g., compounds #906, #1014, #1022 , #1032, etc.) that are analogous to compounds of the instant formula II with the following substituents:
> i. Ring C is a saturated, non-aromatic 10-membered bicyclic moiety;
> ii. R^1 represents C_{1-4}alkyl, C_{1-4}alkoxymethyl;
> iii. n = 0 or 1;
> iv. R^{2a} represents hydrogen."

This ground for rejection is respectfully traversed for several reasons.

First of all, the Schaper '009 compounds all have a **spirocyclic** group in the position of the C-ring of the present compounds, **not** a "saturated, non-aromatic 10-membered **bicyclic** moiety" (emphasis added) as the Examiner asserts. Although the Schaper '009 compounds identified by the Examiner have a two-ring structure attached to X at the 4-position of the quinazoline ring, these two-ring structures are correctly called "1-oxaspiro[2.5]oct-6-yl" and "1,4-dioxaspiro[4.5]dec-8-yl" groups in the Schaper '009 patent.[1] The structures and corresponding names of compounds #906, #1014, #1022 , #1032 relied upon by the Examiner are as follows:

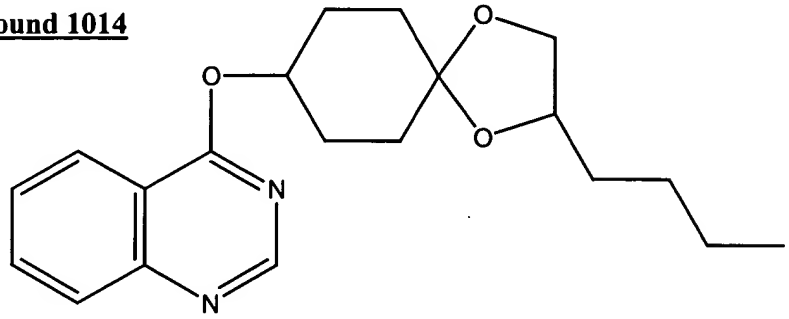
[1] See this nomenclature used for these same groups, *e.g.*, in Preparation Example I (Tabulated Examples 266, 267) at column 34, and in Preparation Example B (Tabulated Example 804) at column 31, of the '009 patent.

Compound 906



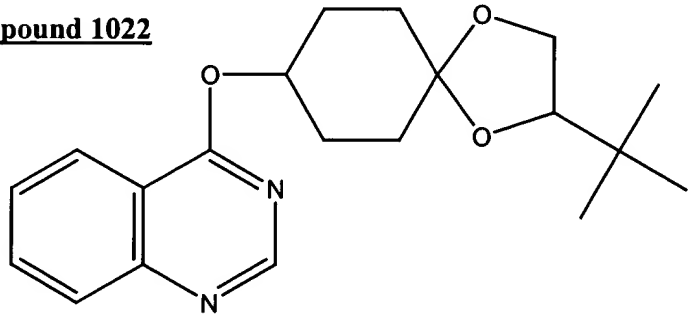
4-(1-Oxa-spiro[2.5]oct-6-yloxy)-quinazoline

Compound 1014



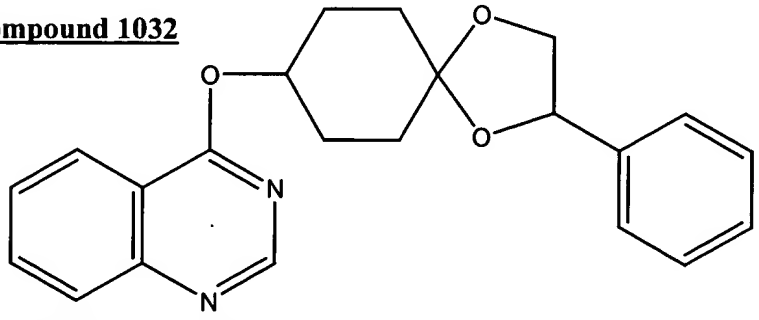
4-(2-Butyl-1,4-dioxa-spiro[4.5]dec-8-yloxy)-quinazoline

Compound 1022



4-(2-*tert*-Butyl-1,4-dioxa-spiro[4.5]dec-8-yloxy)-quinazoline

Compound 1032



4-(2-Phenyl-1,4-dioxa-spiro[4.5]dec-8-ylmethyl)-quinazoline

In accordance with IUPAC nomenclature of organic chemistry (as well as accepted usage), molecules where two rings share **one carbon atom** are called "**spirocyclic**," such as the Schaper '009 compounds, whereas the term "**bicyclic**" is reserved for those compounds that share **two or more carbon atoms**. This "spirocyclic" nomenclature is consistently used in the Schaper '009 patent when naming disclosed compounds, and all 1074 examples tabulated in Tables I through 12 have two rings **which share only one carbon atom** at the position of the C-ring in the present compounds. See also the attached succinct summary of this fundamental difference between spirocyclic and bicyclic, as well as the support from attached pages"IUPAC Nomenclature of Organic Chemistry, Sections A, B, C, D, E, F and H, 1979 Edition, Pergamon Press, ISBN 0-08-022369-9," stating at page 31 that "systems consisting of two rings only, having two or more atoms in common, take the name of an open chain hydrocarbon containing the same total number of carbon atoms preceded by the prefix 'bicyclo-'", and stating at page 37 that "a 'spiro union' is one formed by a single atom which is the only common member of two rings" (emphasis added). See also the attached pages from "A Guide to IUPAC Nomenclature of Organic Compounds, Recommendations 1993, Blackwell Scientific Publications, ISBN 0-632—3488-2," particularly page 52 illustrating spiro structures.

In contrast, all compounds of the present invention, as exemplified in the Examples 1 through 325, have a "bicyclic" or "tricyclic" structure for the C-ring, wherein each of the two or three rings **shares two adjacent carbon atoms** with at least one other ring.

Moreover, the values for the R^1 substituent on ring C do not include anything that could form a spirocyclic group. The specific values that are listed first in the definition of R^1

in claim 39 do not include such a group; even the C_{3-7}alkylene substituent must be joined to two ring carbon atoms, and if R^1 is $R^{56}X^{10}$ then X^{10} cannot be nothing – its minimum value is a direct bond which then prohibits the formation of a spirocyclic group.

Therefore, on this ground alone, it is respectfully submitted that the compounds of the present invention (before and after the above claim amendments) are structurally and patentably distinct from the compounds of the Schaper '009 Patent, and are not at all analogues thereof, as the Examiner has asserted in supporting the rejection.

Secondly, the above amendment to claim 39 defines the C-ring as "a 9 or 10-membered heteroaromatic bicyclic moiety which contains 1-3 heteroatoms selected independently from O, N and S." To the contrary, the spirocyclic ring structure on the "X" at the 4-position of the quinazoline in the Schaper '009 Patent, as the Examiner recognizes in the rejection, are saturated, non-aromatic rings. For this reason as well, the presently claimed compounds are structurally and patentably distinct from the compounds of the Schaper '009 Patent.

Thirdly, the undersigned takes issue with the Examiner's assertion that the Schaper '009 patent is analagous prior art, and therefore believes that this patent is not a proper reference for this obviousness rejection. The relevant case law, some of which is discussed in MPEP §2141(a), provides that a reference, to be relied upon as the basis for an obviousness rejection, must either (1) be in the field of applicant's endeavor or, if not, (2) then be reasonably pertinent to the particular problem with which the inventor was concerned. See, *e.g.*, *In re Oetiker*, 977 F.2d 1443, 1446, 24 USPQ2d, 1443, 1445 (Fed. Cir. 1992). A reference is reasonably pertinent if, even though it may be in a different field from that of the

inventor's endeavor, it is one which, because of the matter with which it deals, logically would have commended itself to an inventor's attention in considering his problem." *In re Clay*, 966 F.2d 656, 659, 23 USPQ2d 1058, 1060-61 (Fed. Cir. 1992). The Examiner points to the passage of the '009 patent at column 19, lines 13-21, in which the field of the invention is characterized:

> "The active substances are suitable for controlling animal pests, in particular insects, arachnids, helminths and mullusks, very particularly preferably for controlling insects and arachnids, encountered in agriculture in livestock breeding, in forestry, in the protection of stored products and materials, and in the hygiene field, are well tolerated by plants and have favorable toxicity to warm-blooded species. They are active against normally sensitive and resistant species and against all or some stages of development."

The specification then continues with an extensive listing of "pests" against which the invention is effective. It is thus clear from this passage and the '009 patent as a whole that the disclosed compounds have the effect of controlling plant and animal pests that are in the environment of the plants or animals, and in that manner affecting the "hygiene" or cleanliness of that environment.

The present invention, by contrast, is not directed toward the eradication of plant and animal "pests", but rather is directed toward pharmaceutical compositions that inhibit VEGF receptor tyrosine kinase activity in a warm-blooded animal to which it is administered, having as one objective the production of an antiangiogenic and/or vascular permeability reducing effect.

It is therefore apparent that the '009 reference is not "in the field of applicants' endeavor" and, moreover, is not "reasonably pertinent to the particular problem with which the inventor was concerned." In particular, one cannot possibly assert that the subject matter

of the '009 reference "logically would have commended itself to an inventor's attention in considering his problem."

It is therefore respectfully submitted that the presently claimed compounds are structurally and patentably distinct from the compounds disclosed in the '009 reference, as detailed under the first and second points stated above, and for these reasons alone this ground for rejection should be withdrawn. However, if the Examiner persists in this rejection, applicants reserve the right to further develop the non-analogous art issue raised as the third point above, if this rejection nevertheless proceeds through further prosecution and/or appeal.

Conclusion

In view of the above amendments to the claims and the foregoing remarks, it is believed that all outstanding grounds for rejection have been fully addressed and overcome, and that all claims are now in condition for allowance. It is therefore respectfully requested all grounds for rejection be withdrawn, and that all claims be allowed.

Information Disclosure Statement

The Examiner's attention is called to the Information Disclosure Statement that is being filed together with this Response, which is accompanied by a form PTO-1449 and a copy of the document listed thereon. It is respectfully requested that these documents be considered, and that such consideration be acknowledged by the Examiner's initials where indicated and return of an initialed copy of the form PTO-1449 to the undersigned.

EXCEPT for issue fees payable under 37 C.F.R. § 1.18, the Director is hereby authorized by this paper to charge any additional fees during the entire pendency of this

application including fees due under 37 C.F.R. §§ 1.16 and 1.17 which may be required, including any required extension of time fees, or credit any overpayment to Deposit Account 50-0310. This paragraph is intended to be a **CONSTRUCTIVE PETITION FOR EXTENSION OF TIME** in accordance with 37 C.F.R. § 1.136(a)(3).

Respectfully Submitted,
Morgan Lewis & Bockius LLP

Date: July 14, 2004 By: _____

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DJB:mk

Rule A-28. Radical Names for Fused Cyclic Systems with Side Chains

28.1—Radicals formed from hydrocarbons consisting of polycyclic systems and side chains are named according to the principles of the preceding rules.

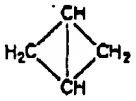
BRIDGED HYDROCARBONS

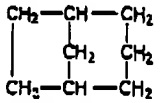
EXTENSION OF THE VON BAEYER SYSTEM

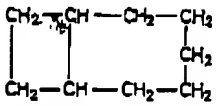
Rule A-31. Bicyclic Systems

31.1—Saturated alicyclic hydrocarbon systems consisting of two rings only, having two or more atoms in common, take the name of an open chain hydrocarbon containing the same total number of carbon atoms preceded by the prefix "bicyclo-". The number of carbon atoms in each of the three bridges* connecting the two tertiary carbon atoms is indicated in brackets in descending order.

Examples:

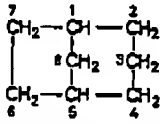

Bicyclo[1.1.0]butane

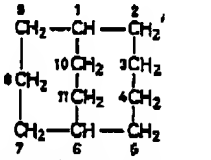

Bicyclo[3.2.1]octane


Bicyclo[5.2.0]nonane

31.2—The system is numbered commencing with one of the bridgeheads, numbering proceeding by the longest possible path to the second bridgehead; numbering is then continued from this atom by the longer unnumbered path back to the first bridgehead and is completed by the shortest path from the atom next to the first bridgehead.

Examples:


Bicyclo[3.2.1]octane

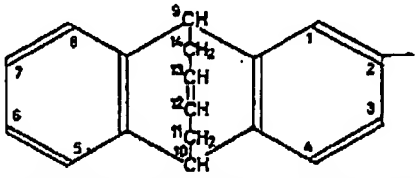

Bicyclo[4.3.2]undecane

Note: Longest path 1, 2, 3, 4, 5
Next longest path 5, 6, 7, 1
Shortest path 1, 8, 5

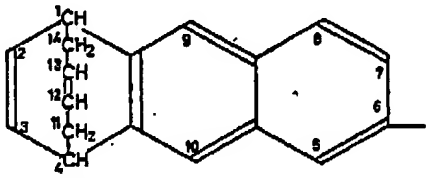
*A bridge is a valence bond or an atom or an unbranched chain of atoms connecting two different parts of a molecule. The two tertiary carbon atoms connected through the bridge are termed "bridgeheads".

34.5—Names for radicals derived from the bridged hydrocarbons considered in Rule A–34.1 are constructed in accordance with the principles set forth in Rule A–24. The abbreviated radical names naphthyl, anthryl, phenanthryl, naphthylene, etc., permitted as exceptions to Rules A–24.2 and A–24.4, are replaced in such cases by the regularly formed names naphthalenyl, anthracenyl, phenanthrenyl, naphthalenediyl, *etc.*

Examples:



9,10-Dihydro-9,10-[2]butenoanthracen-2-yl

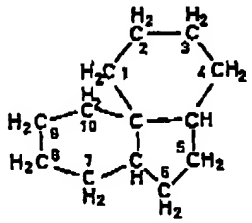


1,4-Dihydro-1,4-[2]butenoanthracen-6-yl

SPIRO HYDROCARBONS

A " spiro union " is one formed by a single atom which is the only common member of two rings. A " free spiro union " is one constituting the only union direct or indirect between two rings*. The common atom is designated as the " spiro atom ". According to the number of spiro atoms present, the compounds are distinguished as monospiro-, dispiro-, trispiro-compounds, *etc.* The following rules apply to the naming of compounds containing free spiro unions.

* An example of a compound where the spiro union is *not* free is:

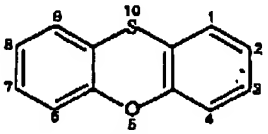


This compound is named by previous rules as dodecahydrobenz[*e*]indene.

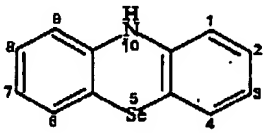
R-2.4.1.4 There are several methods that can be used to derive semisystematic names for heterocyclic components of fused ring systems.

R-2.4.1.4.1 Heterotricyclic ring systems consisting of two benzene rings *ortho*-fused to a 1,4-diheteroatomic six-membered monocyclic ring in which the heteroatoms are different are named by adding the prefix 'pheno-' to the Hantzsch–Widman name of the heteromonocycle (see R-2.3.3.3)[28].

Examples:



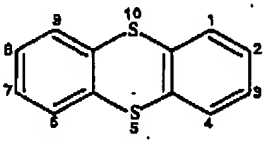
Phenoxathiine



10*H*-Phenoselenazine

R-2.4.1.4.2 Heterotricyclic ring systems consisting of two benzene rings *ortho*-fused to a 1,4-diheteroatomic six-membered monocyclic ring in which the heteroatoms are the same are named by adding the replacement prefix for the heteroatom (see Table 3) to the term '-anthrene', with elision of an 'a'. As exceptions, the names 'phenazine' and 'phenomercurine' are retained.

Example:



Thianthrene

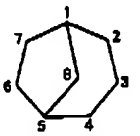
R-2.4.2 **Bridged parent hydrides – extension of the von Baeyer system**

R-2.4.2.1 ***Bicyclic ring systems.*** Saturated homogeneous bicyclic systems having two or more atoms in common, are named by prefixing 'bicyclo-' to the name of the acyclic parent hydride that has the same total number of skeletal atoms; heteroatoms in an otherwise hydrocarbon system are indicated by replacement nomenclature using 'a' prefixes (see R-9.3). The number of skeletal atoms in each of the three acyclic chains (bridges) connecting the two common atoms (bridgeheads[29]) is given by arabic numbers cited in descending numerical order separated by full stops and enclosed in square brackets.

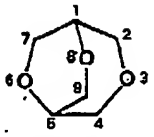
The system is numbered starting with one of the bridgeheads and proceeding through the longest bridge to the second bridgehead, continuing back to the first bridgehead by means of the longer unnumbered bridge; these two bridges constitute the 'main ring' of the system. Numbering is completed by numbering the remaining bridge (the shortest) beginning with the atom next to the first bridgehead.

[28] In names containing the prefix 'pheno-' associated with a Hantzsch–Widman name, the final 'o' is optional.
[29] A 'bridge' is a valence bond, an atom, or an unbranched chain of atoms connecting two different atoms that are already part of a cyclic system of atoms. The two skeletal atoms connected by the bridge are called 'bridgeheads'.

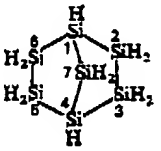
Examples:



Bicyclo[3.2.1]octane



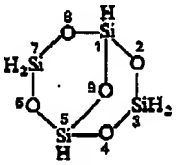
3,6,8-Trioxabicyclo[3.2.2]nonane



Bicyclo[2.2.1]heptasilane

This method has also been used for bicyclic systems of alternating skeletal atoms.

Example:

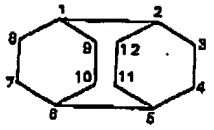


Bicyclo[3.3.1]tetrasiloxane

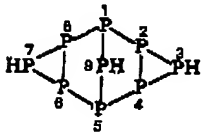
R-2.4.2.2 ***Polycyclic ring systems***[30]. Polycyclic analogues of saturated bicyclic ring systems (see R-2.4.2.1) are named by using the prefixes 'tricyclo-', 'tetracyclo-', etc., in place of 'bicyclo-'. The number of atoms in the additional bridges (called 'secondary bridges') is indicated by arabic numbers separated by full stops and cited, in decreasing numerical order, following those describing the largest bicyclic system. The location of each secondary bridge is indicated by the arabic number locants of the structure already numbered, which are cited as superscripts to the arabic number denoting its length and separated by a comma. When there are secondary bridges of equal length, they are cited in order of the increasing value of their lower-numbered bridgehead atom. The secondary bridges are numbered in decreasing order of size. Numbering of each bridge follows from the bridgehead already numbered proceeding from its higher numbered end. If bridges of equal lengths are present, numbering begins with the bridge having the highest numbered bridgehead atom.

[30] This subsection illustrates the extension of the von Baeyer system to polycyclic systems. For more details, see Rule A-32, in the IUPAC *Nomenclature of Organic Chemistry*[1].

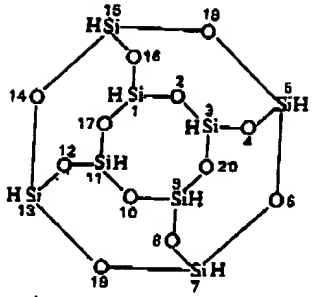
Examples:



Tricyclo[4.2.2.2^{2,5}]dodecane

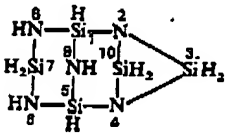


Tetracyclo[3.3.1.0^{2,4}.0^{6,8}]nonaphosphane



Pentacyclo[9.5.1.1^{3,9}.1^{5,15}.1^{7,13}]octasiloxane

Prefixes such as *1Si-* and *1N-* are used in polycyclic systems of alternating skeletal atoms when it is necessary to indicate the atom at the bridgehead that is to have the locant '1'.



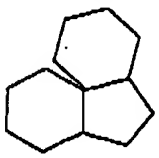
1Si-Tricyclo[3.3.1.1^{2,4}]pentasilazane

R-2.4.3 **Spiro parent hydrides**

A 'spiro union' is a linkage between two rings consisting of a single atom common to both. A 'free spiro union' is a linkage that constitutes the only union direct or indirect between the two rings[31]. The common atom is designated as the 'spiro atom'. According to the number of spiro atoms present, the compounds are distinguished as monospiro, dispiro, trispiro, etc., ring systems. The following recommendations apply only to the naming of parent hydrides containing free spiro unions[32].

R-2.4.3.1 ***Monospiro parent hydrides*** consisting of two homogeneous saturated monocyclic rings are named by placing 'spiro' before the name of the acyclic parent hydride with the same total number of skeletal atoms; heteroatoms, if any, in an otherwise hydrocarbon structure are designated by replacement nomenclature, i.e., by 'a' prefixes (see R-9.3)

[31] An example of a compound where the spiro union is not free is:

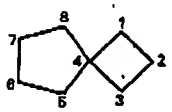


[32] In earlier editions of the IUPAC *Nomenclature of Organic Chemistry*, two methods were described for the naming of spiro parent hydrides (see Rules A-41 and 42, pp. 38–41 and Rules B-10 and 11, pp. 72–73 in the 1979 edition[1]). In these recommendations, only the first of these methods has been retained.

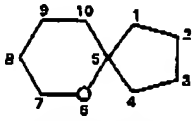
placed before the spiro prefix. The numbers of skeletal atoms linked to the spiro atom in each ring are indicated by arabic numbers separated by a full stop, cited in ascending order, and enclosed in square brackets; this descriptor is placed between the spiro prefix and the name of the parent hydride. R-2.

Numbering starts with a ring atom next to the spiro atom and proceeds first through the smaller ring, if one is smaller, and then through the spiro atom and around the second ring.

Examples:



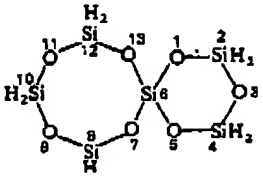
Spiro[3.4]octane



6-Oxaspiro[4.5]decane

The method is also used for monospiro systems of alternating skeletal atoms.

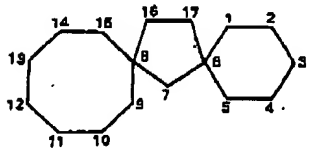
Example:



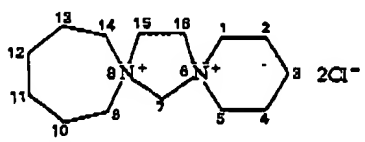
Spiro[5,7]hexasiloxane

R-2.4.3.2 ***Polyspiro parent hydrides*** consisting of unbranched assemblies of three or more saturated homogeneous monocyclic rings are named by using the prefixes 'dispiro-', 'trispiro-', 'tetraspiro-', etc., instead of 'spiro-' in front of the name of the acyclic parent hydride that has the same total number of skeletal atoms. Heteroatoms in an otherwise hydrocarbon system are designated by replacement nomenclature using 'a' prefixes (see R-9.3). The numbers of skeletal atoms linked to the spiro atom in each terminal ring and between the spiro atoms in the other rings are given by arabic numbers separated by full stops cited in the same order as the numbers proceed around the ring and enclosed in square brackets. Numbering begins with a ring atom next to the terminal spiro atom of the smaller terminal ring, proceeding around that terminal ring through its terminal spiro atom and, by the shortest path, through each of the other spiro atoms, around the other terminal ring, and then back to the first terminal ring. R-2.4.4

Examples:



Dispiro[5.1.7.2]heptadecane

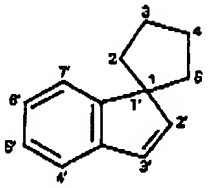


6,8-Diazoniadispiro[5.1.6.2]hexadecane dichloride R-2.4.4.1

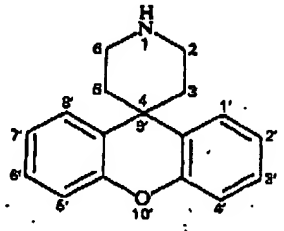
Note: Extension of this procedure to branched polyspiro systems may lead to ambiguity.

R-2.4.3.3 ***Spiro parent hydrides containing polycyclic ring systems***, such as a fused ring system, are named by placing the prefix 'spiro-', 'dispiro-', 'trispiro-', etc., in front of the names of the components, which are cited in order of occurrence beginning with the terminal component earliest in alphabetical order, and enclosed in square brackets. Established numbering of each component is retained, but those of the second cited and succeeding components are primed serially.

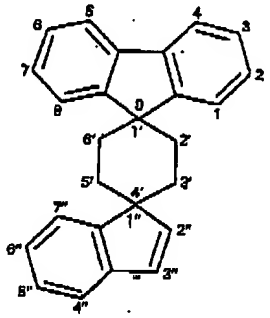
Examples:



Spiro[cyclopentane-1,1′-indene]



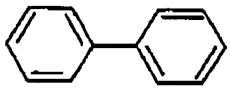
Spiro[piperidine-4,9′-xanthene]



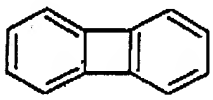
Dispiro[fluorene-9,1′-cyclohexane-4′,1″-indene]

R-2.4.4 **Ring assemblies**

Two or more identical cyclic systems (whether mono- or bicyclic) directly joined to each other by double or single bonds are called 'ring assemblies' when the number of such direct ring junctions is one less than the number of cyclic systems involved.



Ring assemblies



Fused polycyclic system

R-2.4.4.1 ***Assemblies of two identical cyclic systems*** are named in one of two ways: (a) by placing the prefix 'bi-' before the name of the corresponding substituent group (see R-2.5) enclosed in parentheses, if necessary (additive operation); or (b) by placing the prefix 'bi-' before the name of the corresponding parent hydride enclosed in parentheses[33], if necessary (conjunctive operation).

[33] Parentheses may avoid confusion with von Baeyer names.